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By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

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Certifying Officer

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Pharmaceutical Compositions

INCORPORATION BY REFERENCE

The content of US application nos. 60/437,516, filed December 30, 2002; and US application no. 60/441,335 filed January 21, 2003 are incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to drug-containing compositions, pharmaceutical compositions comprising such drugs, and methods for preparing same.

BACKGROUND OF THE INVENTION

Drugs in pharmaceutical compositions can be prepared in a variety of different forms. Such drugs can be prepared so as to have a variety of different chemical forms including chemical derivatives or salts. Such drugs can also be prepared to have different physical forms. For example, the drugs may be amorphous or may have different crystalline polymorphs, perhaps existing in different solvation or hydration states. By varying the form of a drug, it is possible to vary the physical properties thereof. For example, crystalline polymorphs typically have different solubilities from one another, such that a more thermodynamically stable polymorph is less soluble than a less thermodynamically stable polymorph. Pharmaceutical polymorphs can also differ in properties such as shelf-life, bioavailability, morphology, vapor pressure, density, color, and compressibility. Accordingly, variation of the solvation state of a drug is one of many ways in which to modulate the physical properties thereof.

A solvate may be defined as a compound formed by solvation, for example as a combination of solvent molecules with molecules or ions of a solute. Well known solvent molecules include water, alcohols and other polar organic solvents. Alcohols include methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, and t-butanol. Alcohols also include polymerized alcohols such as polyalkylene glycols (e.g.,

polyethylene glycol, polypropylene glycol). The best-known and preferred solvent is typically water, and solvate compounds formed by solvation with water are termed hydrates.

Propylene glycol (1,2-propanediol) is a known substance which is a liquid at ambient temperature. As far as the applicants are aware, propylene glycol is not generally well-known for use in the formation of solvates. US Pat. No. 3,970,651 does disclose the use of propylene glycol in the formation of a crystalline cephalosporin derivative. According to this disclosure a propylene glycolate derivative of a specific cephalosporin zwitterion may be formed in the presence of propylene glycol at acidic pH. This disclosure indicates that the propylene glycol derivative is more stable in solid form than the corresponding ethanolate, especially having excellent colour stability and thermal stability. No other solvates are disclosed in this US patent other than the specific solvate of cephalosporin.

In pharmaceutical formulations certain chemical classes of drugs pose particular problems in preparing pharmaceutical formulations for medical use. One such problem arises in the case of hygroscopic drugs, which tend to absorb water from the air. This is disadvantageous because it makes storage of the drug difficult and can cause degradation of the drug in some cases. Such compounds must be handled in controlled humidity environments during manufacture in order to prevent potency errors due to the changing weight of the drug. The final product must be packaged in individual moisture resistant blisters in order to prevent changes in or degradation of the product. Another problem arises from variable hydration states: molecules may change to a more or less stable form as water, a volatile liquid, is lost. Such changes have been known to cause some hydrates to become amorphous. Likewise, absorption of water by a hygroscopic molecule can plasticise the system and lead to recrystallization as a less stable polymorph.

SUMMARY OF THE INVENTION

Solvates are rarely used in pharmaceuticals because the solvents are usually volatile thus making it difficult to maintain the solvent in the crystal. If one were to desolvate a

pharmaceutical solvate or if it desolvated due to storage conditions or otherwise, it could lead to the formation of multiple polymorphs or complete collapse of the crystal structure, forming an amorphous compound with different physical properties. Obviously, this batch-to-batch variability and questionable shelf life is undesired. Typically people find solvates of common solvents, such as propanol and ethanol. Propylene glycol is similar in structure to propanol, but is not thought of as a solvent. Propylene glycol solvates of the present invention desolvate only at considerably higher temperatures and harsher conditions than traditional solvates. Propylene glycol solvates are also pharmaceutically acceptable in much larger amounts thanone would expose people to with a traditional solvate. Thus, the propylene glycol solvates of the present invention have characteristics that are vastly superior to traditional solvates.

It has now been found that amorphous, crystalline, hygroscopic, or poorly soluble drugs can be made more soluble, more stable, and less hygroscopic and can be prepared simply, reliably and inexpensively.

In a first aspect, the present invention provides a pharmaceutical composition comprising a propylene glycol solvate of a drug which is hygroscopic or has low aqueous solubility. It has surprisingly been found that by using propylene glycol to form a solvate of a hygroscopic drug, the hygroscopicity of the drug is decreased and/or the stability and aqueous solubility is increased. The drug is therefore much easier to formulate and store than its counterpart untreated or hydrated form.

A number of advantages have been found from the use of propylene glycol in this way. First of all, a higher temperature is required to remove propylene glycol as compared with water or ethanol. This therefore results in an increased thermal stability. Thus the invention further relates to methods of making a pharmaceutical solvate more stable at high temperatures by making a PG solvate of the drug. Secondly, propylene glycol solvates are generally more pharmaceutically acceptable than other common solvates, including those formed from alcohols other than ethanol. It has further been found that

the PG solvates of the present invention have fewer solvation states than hydration states. This is beneficial because production and quality of a drug can be more predictable and consistent. Thus an aspect of the present invention relates to methods of reducing the number of hydration states by making a PG solvate of a drug. PG solvates are also beneficial in addressing the problem of polymorphism. Thus an aspect of the present invention relates to methods of reducing the rate and extent a drug changes form and methods of reducing the chance of making an unwanted form because the PG solvates drive production of a single form. Another aspect of the present invention relates to changing the crystal habit of the drug crystal and preventing a drug crystalline habit from changing to a different habit.

The invention relates to making a pharmaceutical that can be made as a hydrate, more soluble or stable by forming a PG solvate of the drug.

The invention further relates to making a pharmaceutical more stable in a humid environment by making a PG solvate of the drug.

The invention further relates to making a crystalline compound from a pharmaceutical that does not readily crystallize by making a crystalline PG solvate of the drug.

The invention further relates to increasing the solubility of a crystalline pharmaceutical by making a PG solvate of the drug.

The invention further relates to methods of lowering the amount of drug solvation during wet granulation by making a PG solvate of the drug.

A particularly important aspect of the present invention is the realization that formation of propylene glycol solvates is applicable in a general way to drugs whereby the above advantages may be conferred. For example, the invention further relates to reducing the level of hygroscopicity of a pharmaceutical metal salt (crystalline, amorphous, solvate